stright chain C_{1-6} alkyl or a straight chain C_{2-6} alkenyl having an ether link or an ester link, toluenyl, COOH, nitrate, or halide (Br, Cl, I, F), wherein at least one of R and R_1 is COOH, wherein R_2 and R_3 are independently hydrogen, sulfamide, carboxyamide, cyano, straight or brnched C_{1-6} alkyl, straight or branched C_{2-6} alkynyl, straight or branched C_{1-6} alkoxy, a stright chain C_{1-6} alkyl or a straight chain C_{2-6} alkenyl having an ether link or an ester link, toluenyl, COOH, nitrate, or halide (Br, Cl, I, F),

with the proviso that if either R or R_1 is CH_3, the other is not H or CH_3; and

with the further proviso that if either of R or R_1 is 2-methyl, the other is not 4-alkoxycarbonyl.

Please add the following new claims 33-35.

33. (New) The ischemia-damage mitigating salt of claim 1, wherein R and R_1 are meta to each other and to the heteroatom.

34. (New) The ischemia-damage mitigating salt of claim 23, wherein R_2 and R_3 are both hydrogen.

35. (New) The ischemia-damage mitigating salt of claim 24, wherein R and R_1 are each COOH.

Remarks

Claims 1, 5-21 and 28-35 are pending in this application. Claims 1, 7, 14 and 28 have been amended and claims 33-35 have been added to more particularly point out and distinctly claim the invention. Additionally, the specification has been amended to eliminate reference to AP5.

Applicants acknowledge with appreciation the allowance of claims 8-13, 15-21, 29, 30 and 32. Claims 1, 5-7, 14, 28 and 31 stand rejected. Applicants respectfully request reconsideration and withdrawal of the current rejections based on the above claim amendments and the discussion below.

Rejections under 35 U.S.C. 112

Claims 1, 5-7 and 14 stand rejected under 35 U.S.C. 112, first paragraph. It is asserted that the subject matter of the claims, particularly the description of the 3,5 dicarboxy compound, was not described in the application as filed. Applicants note that the dicarboxy compound is no longer specifically claimed in the rejected claims. Applicants do note that the 3,5 dicarboxy embodiment is encompassed within the scope of generic claim 1, and Applicants do not disclaim that embodiment. However, Applicants assert that the current written description rejection should no longer stand and respectfully request withdrawal of that rejection.

Claims 1 and 5-7 stand rejected under 35 U.S.C. 112, second paragraph as being indefinite for not reciting the required anion and reciting in claim 7 compounds that do not have the 1,3,5 substitution. Applicants note that the amended claim 1 now recites a salt of a compound, and thus does not require an anion. Additionally, claim 1 no longer requires that there be a 1,3,5 substitution. Applicants therefore respectfully request withdrawal of this rejection.

Rejection under 35 U.S.C. 102

Claims 28 and 31 stand rejected under 35 U.S.C. 102(b) as encompassing embodiments that read on compounds described in Tamura. Applicants note that amended claim 28 does not read on the Tamura compounds and therefore respectfully requests withdrawal of this rejection.

Conclusion

In light of the claim amendments and the above discussion, Applicants respectfully request withdrawal of all objections and rejections and passage of the claims to allowance. Should there be any additional matters that prevent allowance of the claim, the Examiner is urged to contact the undersigned attorney.

Respectfully submitted,

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Dated: New York, New York
September 14, 2001

By: _____
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Registration No.: 44,704

Appendix 1

Marked up specification - U.S. Patent Application 09/118,388

Deleted material is bracketed. No material was added.

--Preferred compounds of formula I include, for example, 1-phenacyl-2,3-dicarboxypyridinium bromide; 1-phenacyl-2,4-dicarboxypyridinium bromide; 1-phenacyl-2,5-dicarboxypyridinium bromide; [1-phenacyl-3,5-dicarboxypyridinium bromide (AP5);]1-phenacyl-2,6-dicarboxypyridinium bromide; 1-phenacyl-2,3-dicarboxyimidepyridinium bromide; 1-phenacyl-2,4-dicarboxyimidepyridinium bromide; 1-phenacyl-2,5-dicarboxyimidepyridinium bromide; and 1-phenacyl-2,6-dicarboxyimidepyridinium bromide--.

Delete the first full paragraph, page 35, lines 6-26 through page 36, lines 1-7, and insert therefor the following:

--In an alternative embodiment of the screening assay of Example 3, various concentrations of the test compound (*e.g.* 10-1000 μM) are incubated with the indicator cells in presence of a fixed concentration fo 3-AP (*e.g*, 200 μM). The toxicity of the test compounds may be evaluated in parallel cultures incubated without 3-AP; generally, the desired test compound will show cellular toxicity at much higher doses than thos that confer protection against 3-AP (*e.g.*, 10-10,000-fold). The results of such tests are summarized in Table V, below.

Table V.

Effect of test compounds on 3-AP cytotoxicity

No effect or weakly protective	Toxic or no effect	Protective (50% Effective dose; 50% Toxic dose)
Glial cell assay (HTB14)		
AP6	AP9	[AP5 (150 μM; 7 mM)]
AP2	AP12	p27a (425 μM; 5 mM)
AP7	AP19	AP21 (100 μM; not tested)
YA1	AP20	AP22 (199 μM; 1 mM)
YA2	AP23	
AP18	AP28	
AP24	3,5-di-tert.-butyl-4-hydroxytoluene	
ascorbic acid		
32P		

wherein:

AP6 is N-(2-phenyl-2-oxoethyl)-2-(2'-pyridine)-pyridinium bromide.

AP2 is N-(2-phenyl-2-oxoethyl)-quinolinium bromide.

AP7 is N-(2-phenyl-2-oxoethyl)-pyrazinium bromide.

YA1 is 2-phenyl-2-oxoethyl-dimethylphosphonate.

YA2 is N-(2-phenyl-2-oxoethyl)-triethylammonium bromide.

AP18 is N-(2-phenyl-2-oxoethyl)-4-tert.-butylpyridinium bromide.

AP24 is N-(2-phenyl-2-oxoethyl)-3-n-butylpyridinium bromide.

34P is pyridine-3,5-dicarboxylic acid.

AP9 is N-(2-phenyl-2-oxoethyl)-4-N,N-dimethylamino-pyridinium bromide.

AP12 is N-(2-phenyl-2-oxoethyl)-pyrazinium bromide.

AP19 is N-(2-phenyl-2-oxoethyl)-3-fluoropyridinium bromide.

AP20 is N-(2-phenyl-2-oxoethyl)-4-ethylpyridinium bromide.

AP23 is N-(2-phenyl-2-oxoethyl)-2,6-dihydroxymethylpyridinium bromide.

AP28 is N-(2-phenyl-2-oxoethyl)-3,5-diiodo-4-pyridinone.[

AP5 is N-(2-phenyl-2-oxoethyl)-3,5-dicarboxypyridinium bromide; and this compound has also been coded PICVA-13.]

AP21 is N-(2-phenyl-2-oxoethyl)-3,4-dicarboxyamide-pyridinium bromide.

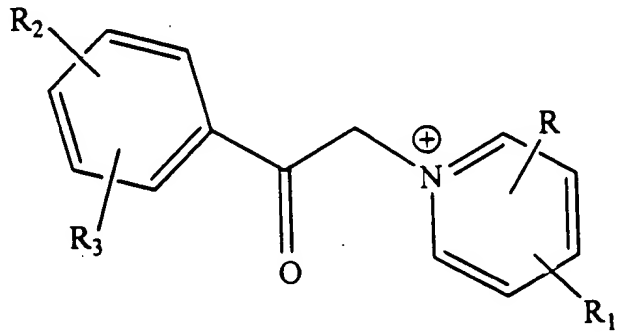
AP22 is N-(2-phenyl-2-oxoethyl)-3-bromo-5-carboxypyridinium bromide.--

Appendix 2

Marked up amended claims - U.S. Patent Application 09/118,388

Added material is underlined; deleted material is bracketed.

1. (Three times amended) An ischemia-damage mitigating salt of a compound, said compound having a formula I:



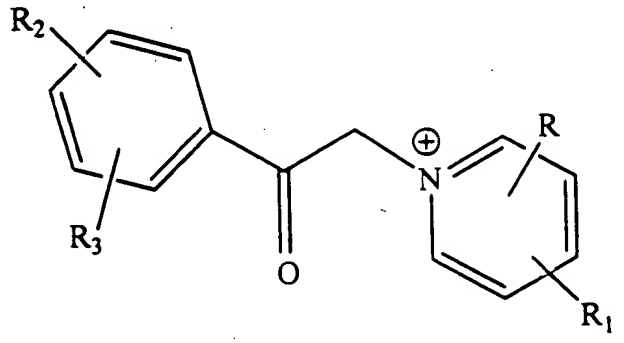
wherein R and R_1 are independently hydrogen, sulfamide, carboxyamide, cyano, straight or brnched C_{1-6} alkyl, straight or branched C_{2-6} alkynyl, straight or branched C_{1-6} alkoxy, a stright chain C_{1-6} alkyl or a straight chain C_{2-6} alkenyl having an ether link or an ester link, toluenyl, COOH, nitrate, or halide (Br, Cl, I, F), wherein at least one of R and R_1 is COOH, wherein R_2 and R_3 are independently hydrogen, sulfamide, carboxyamide, cyano, straight or brnched C_{1-6} alkyl, straight or branched C_{2-6} alkynyl, straight or branched C_{1-6} alkoxy, a stright chain C_{1-6} alkyl or a straight chain C_{2-6} alkenyl having an ether link or an ester link, toluenyl, COOH, nitrate, or halide (Br, Cl, I, F)[, wherein R and R_1 are meta to each other and to the heteroatom].

7. (Twice amended) The ischemia-damage mitigating salt of claim 1 wherein the compound is selected from the group consisting of 1-phenacyl-2,3-dicarboxypyridinium bromide; 1-phenacyl-2,4-dicarboxypyridinium bromide; 1-phenacyl-2,5-dicarboxypyridinium bromide; [1-phenacyl-3,5-dicarboxypyridinium bromide (AP5);]1-phenacyl-2,6-dicarboxypyridinium bromide; 1-phenacyl-2,3-dicarboxyimidepyridinium bromide; 1-phenacyl-2,4-dicarboxyimidepyridinium bromide;

1-phenacyl-2,5-dicarboxyimidepyridinium bromide; and 1-phenacyl-2,6-dicarboxyimidepyridinium bromide.

14. (Twice amended) The pharmaceutical composition of claim 8 wherein the compound is selected from the group consisting of 1-phenacyl-2,3-dicarboxypyridinium bromide; 1-phenacyl-2,4-dicarboxypyridinium bromide; 1-phenacyl-2,5-dicarboxypyridinium bromide; [1-phenacyl-3,5-dicarboxypyridinium bromide (AP5);]1-phenacyl-2,6-dicarboxypyridinium bromide; 1-phenacyl-2,3-dicarboxyimidepyridinium bromide; 1-phenacyl-2,4-dicarboxyimidepyridinium bromide; 1-phenacyl-2,5-dicarboxyimidepyridinium bromide; and 1-phenacyl-2,6-dicarboxyimidepyridinium bromide.

28. (Amended) An ischemia-damage mitigating compound or salt thereof, said compound having a formula I:



wherein R and R_1 are independently hydrogen, sulfamide, carboxyamide, cyano, straight or brnched C_{1-6} alkyl, straight or branched C_{2-6} alkynyl, straight or branched C_{1-6} alkoxy, a stright chain C_{1-6} alkyl or a straight chain C_{2-6} alkenyl having an ether link or an ester link, toluenyl, COOH, nitrate, or halide (Br, Cl, I, F), wherein at least one of R and R_1 is COOH, wherein R_2 and R_3 are independently hydrogen, sulfamide, carboxyamide, cyano, straight or brnched C_{1-6} alkyl, straight or branched C_{2-6} alkynyl, straight or branched C_{1-6}

alkoxy, a stright chain C_{1-6} alkyl or a straight chain C_{2-6} alkenyl having an ether link or an ester link, toluenyl, COOH, nitrate, or halide (Br, Cl, I, F),

with the proviso that if either R or R_1 is CH_3, the other is not H or CH_3; and

with the further proviso that if either of R or R_1 is 2-methyl, the other is not 4-alkoxycarbonyl.